# In-vivo Devices for the Detection of Cervical Cancer and its Precursors:
## Submission Guidance for an IDE
## Draft Document

**This guidance document is being distributed for comment purposes only.**

**Obstetrics and Gynecology Devices Branch**
**Division of Reproductive, Abdominal, Ear, Nose and Throat, and Radiological Devices**
**Office of Device Evaluation**

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Comments and suggestions regarding this draft document should be submitted within 90 days of the above release date to Mridulika Virmani, Ph.D., Obstetrics and Gynecology Devices Branch, Office of Device Evaluation, 9200 Corporate Bouleward (HFZ-470), Rockville, MD 20850. Comments and suggestions received after this date may not be acted upon by the Agency until the document is next revised or updated. For questions regarding the use or interpretation of this guidance draft document, contact Colin M. Pollard at (301) 594-1180 or by E-mail at CMP@CDRH.FDA.GOV.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
Center for Device and Radiological Health

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## INTRODUCTION

This guidance is intended to identify the elements that the Food and Drug Administration (FDA), Center for Devices and Radiological Health (CDRH), Office of Device Evaluation (ODE) would expect to see in an Investigational Devices Exemptions (IDE) application for an in vivo device for the detection of cervical cancer or its precursors (hereinafter referred to as in vivo detection devices). These devices may use many different techniques such electrical and optical signals, or fluorescence or Raman spectroscopy for the in vivo detection of cervical cancer or its precursors. It is important to understand that devices based on certain technologies may not require all of the information contained herein, whereas devices based on other technologies may require additional studies beyond the scope of this guidance document.

For general information about how to submit an IDE application, contact FDA's Center for Devices and Radiological Health's (CDRH) Division of Small Manufacturers Assistance (DSMA) at (800) 638-2041 or (301) 443-6597. FDA welcomes comments on this draft guidance document and will consider all scientifically valid alternatives to the preclinical and clinical requirements stated within. ***It is also highly recommended that the sponsor of a new investigation contact the Obstetrics and Gynecology Devices Branch (OGDB) within the Office of Device Evaluation (ODE) prior to submission of an original IDE application, at (301) 594-1180.***

This guidance document represents the agency's current thinking on the appropriate content of IDE applications for in vivo devices for the detection of cervical pre-cancer or cancer. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes, regulations, or both.

## INDICATIONS FOR USE

The type of clinical study necessary to support a Premarket approval (PMA ) for an in vivo detection device will depend on the proposed indication for use. Devices that are intended to replace the Papanicolaou (PAP) smear as a primary screening tool will require a different sort of clinical study than a device intended to be used as an adjunct to the PAP smear, or as an aid in triaging patients for colposcopy.

The clinical study section of this guidance discusses the issues surrounding clinical study design for several of the indications that FDA has considered to date. This list does not include all possible indications for these devices. If a manufacturer wishes to design a clinical study for a different indication, FDA is willing to provide interactive feedback on the proposed clinical study design.

## DEVICE DESIGN AND DESCRIPTION

### Underlying Model

Provide a complete description of the underlying model. This should include the following:

1. Physiological basis for the model, with copies of important supporting references
2. Any assumptions inherent in the model
3. How the model was validated (include test protocols, data, and conclusions)

### Principle of Operation

Describe the principle of operation of the device, including:

1. Does the device contact the cervix or it is a non-contact device?
2. Does the device read the entire cervix at once, or does the operator need to manually "scan" the cervix?
3. What are the dimensions of the area that the device "sees"?
4. Can the device "see" the endocervix?
5. How does operator ensure complete examination of the cervix?

### Device Description

Describe how your model was implemented in the device design, including:

1. fully dimensioned engineering drawings
2. block diagram, including all inputs, output, and major processing steps
3. complete characterization of all components
4. description of user interface, including any parameters that the user can set
5. discussion of safety features for patient and operator
6. system-level hazard analysis
7. samples (where feasible) or a videotape showing the device in operation are helpful

### Materials

Provide a complete list of all patient-contacting materials, and where relevant, provide a discussion as to why a given material was chosen for a particular function. If any patient-contacting material contains a color pigment, please provide the following information: chemical composition, color index number, and color additive listing (from 21 CFR 73).

**Biocompatibility Testing (for patient-contacting devices)**

The following biocompatibility testing should be performed on the finished device for all patient-contacting components, as these devices are considered surface device, with a limited duration contact time to mucosal tissues. Tests should be conducted in conformance with Good Laboratory Practices (GLP) in accordance with 21 CFR 58.

1. acute systemic toxicity
2. cytotoxicity
3. sensitization (with both polar and non-polar extracts)
4. irritation (mucosal)

If the device is made of materials that have been well-characterized chemically and physically in the published literature, and have a long history of safe use, FDA will accept adequate justification for not conducting some or all of the suggested tests.

For additional information on biocompatibility, please refer to the Blue Book Memorandum #G95-1 Use of International Standard ISO-10993, ☮Biological Evaluation of Medical Devices Part 1: Evaluation and Testing,' available from DSMA.

**Software**

Provide documentation describing the software development lifecycle and risk management activities. This should include at a minimum:

1. software hazard analysis
2. software requirements specification
3. hardware requirements
4. system level test plan with pass-fail criteria and traceability to requirements
5. results of system level testing
6. summary of software Quality Assurance (QA) activities

If the device will use Off-the-Shelf (OTS) software (e.g., Windows 95, DOS, digital signal processing software provided by a third party, etc.), the following additional information should be provided **for each OTS software component used:**

1. title, manufacturer, version number and date
2. hardware requirements for the OTS software
3. function of the OTS software
4. steps taken to validate intended use of OTS software
5. discussion of why use of OTS software is appropriate given both the function of the OTS software, and the intended use and indications for use of the

device.

Additional guidance on software documentation can be found in "Reviewer Guidance for Computer Controlled Medical Devices Undergoing 510(k) Review", available from DSMA. In addition, a guidance document addressing issues associated with OTS software is currently being developed.

## DEVICE PERFORMANCE

### Laser/optical issues

If the device uses a laser, provide the following:

1. Peak emission wavelength(s)
2. Peak power and average power
3. Identify if it is pulsed or continuous wave
4. If pulsed, provide pulse width and pulse repetition rate
5. Exposure time per site or number of pulses per site
6. Total possible exposure time or maximum f pulse per examination site and total patient
7. Size of irradiation zone

If the device uses a broadband source, provide either:

- Relative spectral output with and absolute total power output measurement;
  or
- Absolute spectral irradiance, measured with a NIST-traceable calibrated spectroradiometer.

In all cases, describe the measurement apparatus and procedure, giving an estimate of the uncertainties associated with the measurement.

If the device emits short wavelength ultraviolet radiation at levels approaching occupational safety limits ( biologically effective radiation cannot exceed 0.003 $J/cm^2$ for UV radiation between 180 nm and 400 nm), carcinogenicity testing may be necessary. We recommend that you contact us as early as possible if your device falls into this category.

### Electrical Safety

Provide either:

- Certification that the device complies with applicable electrical safety standards (e.g., IEC 601-1, UL 2601);

or

- Test results which guarantee a similar level of protection.

**Electromagnetic Compatibility (EMC)**

Provide either:

- Certification that the device complies with applicable EMC standards (e.g., IEC 601-1-2, IEC 801-2,3,4,5, CISPR 11);
  or
- Test results which guarantee a similar level of protection;
  or
- Justification for why this information is unnecessary (e.g., due to device design or working conditions).

## LABELING

Provide samples of all device labeling. The labeling must include the following information (21 CFR 812.5):

1. name and place of business of the manufacturer, packer, or distributor
2. quantity of contents (if appropriate)
3. directions for use
4. reprocessing instructions
5. description of all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions
6. the statement: "CAUTION - Investigational Device, Limited by Federal law to investigational use."

**Note**: 21 CFR 812.5 (b) stipulates that the labeling of an investigational device shall not bear any statement that is false or misleading in any particular and shall not represent that the device is safe or effective for the purposes for which it is being investigated.

## MANUFACTURING

Provide a description of the methods, facilities, and controls used for the manufacture, processing, packaging, and storage of the device, in sufficient detail so that a person generally familiar with Good Manufacturing Practices can make a knowledgeable judgment about the quality systems used in the manufacture of the device.

## STERILIZATION

*Reusable components*

If the device is patient-contacting, discuss the methods used to ensure that there is

no patient-to- patient contamination. If the device contacts the patient, it must either be sterilized between uses, or some sort of disposable sheath should be used. Describe the methods used to validate whatever method is chosen.
For important additional information on reprocessing, please refer to the draft "Labeling Reusable Medical Devices Reprocessing in Health Care Facilities: FDA Reviewer Guidance" (March 1995). A copy of this guidance may be obtained from DSMA.

*Single-use components*

1. Provide the method of sterilization, and the sterility assurance level.
2. Identify the method used to validate the sterilization procedures. If the method is a standard, well-recognized method, simply provide the method.
3. Describe the packaging system that will maintain sterility.
4. If the device is sterilized using ethylene oxide, identify the maximum levels of residues of ethylene oxide, ethylene chlorohydrin and ethylene glycol. If the device is radiation sterilized, identify the radiation dose.

## OTHER REQUIRED INFORMATION (812.20)

*Commercialization.*

Specify whether or not the device is to be sold to the patient during the clinical study. If so, explain why this does not constitute commercialization.

*Environmental Impact.*

Provide either:

- An environmental impact assessment describing the potential environmental impact of manufacturing and investigating the device;
  or
- A claim for categorical exclusion from the requirement, in accordance with 21 CFR 25.24.

## SUMMARY OF ALL PRIOR INVESTIGATIONS

### In vitro and animal testing

Provide a complete description of all in vitro and animal testing. This should include:

1. justification for choice of model
2. comparison of the model used in the study to that proposed to be used in

humans
3. test protocols and methods
4. results (including samples of raw data)
5. conclusions

**Note:** Adequate preclinical test data, demonstrating that the device is safe and that it functions as intended, must be submitted before approval for clinical studies in humans will be granted.

**Clinical Testing**

Provide the following information about all prior clinical investigations involving the device:

1. complete bibliography, including copies of important references
2. summary of unpublished data
3. complete discussion of all known adverse events or device failures

## CLINICAL STUDY - FEASIBILITY

What is the purpose of conducting a Feasibility Study?

⇒ A feasibility study should validate device performance, including its ability to reliably detect cervical cancer and pre-cancer.
⇒ If the device is patient-contacting, this study should also be used be demonstrate that when the device contacts the cervix, it does not damage the tissue, and does not affect the results of subsequent PAP smears or colposcopic examinations.
⇒ A feasibility study would also provide the estimated device effectiveness that would be used for the sample size calculations in the PMA study.

**Sample Clinical Study Plan:**

- Study 100 patients who have previously been found to be PAP+ and are reffered for colposcopy.
- This should include at least 25 patients with a diagnosis of ASCUS, at least 25 patients with a diagnosis of LSIL, and at least 25 patients with a diagnosis of HSIL, so that device effectiveness can be estimated for each group.
- If the device is patient-contacting, do the in vivo detection test, followed by colposcopy, followed by a repeated in vivo detection test. The colposcopy will help detect any trauma to the cervix, and the comparison of the first and second in vivo detection results will detect any effects of the in vivo device on

colposcopy. If the device is not patient-contacting, the second in vivo detection test is not necessary.

- If device traumatizes the cervix or otherwise affects colposcopic examination, an alternate sequence should be designed.
- If the device is intended to localize lesions, colpophotography or a similar technology should be used for documentation. The protocol should precisely describe how the clinician will determine that the device reading and the biopsy were taken from the exact same location.
- Directed cervical biopsy should be done based on the colposcopic examination, as defined in a written protocol. However, if the device is intended to localize a particular lesion, directed biopsy should also be done at the site where the highest reading from the in vivo detection device occurs, or above the pre-determined threshold for in vivo devices, if this site or other sites was not previously identified as a biopsy sites by colposcopy. This will ensure that sites that may be identified by the device, but not by colposcopy, are captured for histologic confirmations.
- A written protocol should be defined for the histological examination of the colposcopy and in vivo device directed biopsies, and the examining pathologist should be blinded as to the method used to select the biopsies.

## CLINICAL STUDY - SAFETY AND EFFECTIVENESS

### Overview

This section will discuss possible safety and effectiveness study designs to support the following indications for in vivo detection devices. Companies that plan to pursue combined indications for use should consider the issues addressed in each applicable section.

1. Use at the time of the PAP smear - Adjunct to the PAP smear for primary screening
2. Use before referral to colposcopy - Triage of patients to colposcopy following an ASCUS PAP smear
3. Use at the time of colposcopy - Adjunct to colposcopic examination to assist in the localization of biopsy sites
4. Use instead of the PAP smear - Replace PAP smear as a primary screening tool.

The study designs presented here represent one possible approach for demonstrating the safety and effectiveness of the device for the proposed indications for use. Alternative study designs will be considered by FDA on a case-by-case basis, FDA will also consider study designs for other of indications for use.

### Common Elements

The following information should be included regardless of the indications for use:

*Study Subject Selection*

**The types of patients selected for inclusion into the clinical study should support the intended and indicated uses claimed for the device. Possible sub-groups that should be included to represent the spectrum of cervical changes found in women as a result of following factors:**

- Premenopausal/menopausal
- Age
- Parity
- Pregnant/non-pregnant
- Previous surgical cervical procedures that might disturb cervical anatomy
- Menstruating/non-menstruating

The studies should specify the minimum education and training necessary for the clinician with colposcopy and with the in vivo device.

*Risk Analysis*

Provide a complete description of all potential risks to the patient. For devices using lasers or other light sources, possible adverse events due to photosensitivity that may be known or unknown to the patient, e.g., drug photosensitivity, should be addressed in this section, as well as other standard risks.

*Informed Consent*

Provide copies of the informed consent forms that will be used during the study. You may consult the "Investigational Device Exemption Manual", available from DSMA, for additional guidance on informed consent.

**Indications for Use 1 - Adjunct to the PAP smear**

*Intended Use*

The in vivo detection device will be used in addition to the PAP smear for primary screening for cervical cancer or its precursors. (Specify if in vivo device is to be used before or after the PAP smear.)

*Description of patient population*

**Inclusion criteria**

Women who are candidates for a PAP smear

**Exclusion criteria**

Total hysterectomy

*Investigational Plan*

**Hypothesis**

The combination of PAP smear and in vivo detection detects more patients with LSIL+ than PAP smear alone, and there is not a significant decrease in specificity.

**Sample Clinical Study Design**

- All patients receive both PAP and in vivo detection device during the primary screening examination. The results of the in vivo detection device are withheld from the clinician until the results of the PAP are available. Also, the pathologist reading the PAP smear should be blinded to the results of the in-vivo device.
- Once the results of the PAP are received, if either the PAP or the device is positive, the patient is scheduled for colposcopy. The study sponsor should justify the written cytologic criteria that will be used to refer the patient to colposcopy for the PAP and threshold criteria used for the in vivo detection device.
- By waiting for the PAP results before scheduling for all patients, possible confounding effects of the time between the screening visit and colposcopy are reduced. The maximum time between screening and colposcopy should be 4 weeks.
- Directed biopsy should be done based on the usual criteria for colposcopic examination, as defined in a written protocol.
- A written protocol should be defined for the histological examination of the directed biopsy, and the examining pathologist should be blinded as to the method used to select the biopsy.

**Study Size**

- Sample size calculations should be based on appropriate statistical techniques and result in adequate power to detect a statistically significant difference between the two methods.
- Study should include at least 3 clinical centers.

*Data Analysis*

- Compare relative sensitivity and positive predictive value of the two devices

for the following 3 categories: ASCUS, LSIL, and HSIL.
- Demonstrate effect (or lack of effect) of patient demographic and clinical characteristics discussed above.

**Indications for Use 2 - ASCUS triage**

*Intended Use*

The in vivo detection device will be used to determine which ASCUS (or ASCUS+LSIL) patients are referred to colposcopy.

*Description of patient population*

**Inclusion criteria**

Women with an ASCUS (or ASCUS + LSIL) PAP within the past 4 weeks

**Exclusion criteria**

None????

*Investigational Plan*

**Hypothesis**

The in vivo detection device can be used to differentiate ASCUS cervices from HSIL cervices or LSIL from HSIL cervices.

**Study Design**

- Patients must have had an ASCUS or LSIL PAP within the past 4 weeks. The study sponsor will have to justify the cytologic cut-off used to refer patients for colposcopy.
- All patients are examined first using the in vivo detection device, and then by standard colposcopic procedures. Justify that in vivo device will not interfere with results of colposcopy.
- Directed biopsy should be done based on the colposcopic examination, as defined in a written protocol.
- A written protocol should be defined for the histological examination of the directed biopsy, and the examining pathologist should be blinded as to the method used to select the biopsy.

**Number of study subjects**

- Sample size calculations should be based on appropriate statistical techniques

and result in adequate power to detect a difference between the two methods.
- Study should include at least 3 clinical centers

*Data Analysis*

The positive predictive value of the ability of the in vivo detection device to identify ASCUS or LSIL) patients with high grade lesions (as determined by directed biopsy) should be calculated.

**Intended Use 3 - Localize Biopsy sites**

*Intended Use*

The in vivo detection device will be used at colposcopy to localize sites for biopsy. (This is clearly only appropriate for those devices with a localization capability)

*Description of patient population*

**Inclusion criteria**

Women who are candidates for colposcopy

**Exclusion criteria**

None?

*Investigational Plan*

**Hypothesis**

The ability of the device to select biopsy sites for high grade lesions is as good as that of colposcopy using acetic acid.

**Study Design**

- Patients must have had an abnormal PAP (either ASCUS or LSIL) within the past 4 weeks. The study sponsor will have to justify the cytologic criteria used to refer patients for colposcopy.
- A colposcopic examination is performed. Biopsy sites are first identified by the device, and colpophotography or a similar technology is used for documentation. The protocol should precisely describe how the clinician will determine that the device reading and the biopsy were taken from the exact same location, and to compare in vivo device results to colposcopy reults.

- Biopsy sites are then located using acetic acid, as defined in a written protocol.
- Directed biopsies are taken from any site identified by either the in vivo device or by acetic acid. The numerical labeling of the biopsies should be randomized, so as to ensure that the pathologist is blinded to the clinical method used to determine the site.
- A written protocol should be defined for the histological examination of the directed biopsy, and the examining pathologist should be blinded as to the method used to select the biopsy.

**Number of study subjects**

- Sample size calculations should be based on appropriate statistical techniques and result in adequate power to detect a difference between the two methods.
- Study should include at least 3 centers

*Data Analysis*

Comparison of sites selected both by colposcopy and readings of in vivo device and areas selected by device that would not be selected by colposcopy.

**Intended Use 4 - Primary screening device**

*Intended Use*

The *in vivo* detection device will be used to replace the PAP as a primary screening device.

*Special issues for consideration:*

- Because the device will be used as a primary screening tools, the sponsor must demonstrate safety and effectiveness in all possible sub-groups of women especially if indications include older women or others with transformation zone that may be obscured into the endocervical canal.
- The study must demonstrate that the device is as good as the PAP, with a high degree of confidence for sensitivity and specificity.
-

The measure of truth will be colposcopy on all PAP ASCUS+ and /or all cases with device readings over the claimed threshold. A proportion of PAP - device - should have colposcopy. All equivocal readings of in vivo device should have colposcopy (with biopsy as indicated).

## RELATED FDA DOCUMENTS

The following related documents are available from the Center for Devices and Radiological Health's (CDRH) Division of Small Manufacturers Assistance (DSMA) at (800) 638-2041 or (301) 443-6597.

Blue Book Memorandum "Use of International Standard ISO-10993, ☮Biological Evaluation of Medical Devices Part 1: Evaluation and Testing"

Reviewer Guidance for Computer Controlled Medical Devices Undergoing 510(k) Review

Labeling Reusable Medical Devices Reprocessing in Health Care Facilities: FDA Reviewer Guidance (March 1995)

Investigational Device Exemption Manual